BECKMAN COULTER

INTEROFFICE MEMORANDUM

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November 18, 1999

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
United States' Food & Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Draft Compliance Guidance Manual:
Inspection of Medical Devices
Second Release for Comments on August 12, 1999

Ladies & Gentlemen,

Beckman Coulter appreciates the opportunity to comment on FDA's "Draft Compliance Guidance Manual: Inspection of Medical Devices" as re-issued for comments on August 12, 1999. This letter provides summary comments regarding the proposal. Comments on specific aspects of the draft guidance are provided in the attached table.

Beckman Coulter is a major international manufacturer and worldwide distributor of medical and scientific test systems, including *in vitro diagnostic* (IVD) test systems. The company was formed in October 1997 by the combination of what was then Beckman Instruments, Inc., based in Fullerton, California and Coulter Corporation, based in Miami, Florida. Beckman Coulter headquarters are located in Fullerton, California, with manufacturing facilities located in Fullerton, Brea, Carlsbad, and Palo Alto, California; Miami, Florida; and Galway, Ireland. The company's 1998 sales totaled $1.7 billion.

Beckman Coulter generally supports both the Draft Guidance and QSIT inspectional approach, but the Company has a few general comments, which follow. Specific comments on the document appear in the attached table.

The Draft Guidance is, in several places, confusing in regard to the distinction between manufacturing and design controls. Many large manufacturers have centralized design and validation activities in one location, with manufacturing and related process validation occurring at one or more remote manufacturing sites. The Corrective and Preventative Action (CAPA) system may be similarly split. This draft does not adequately clarify that all inspectional issues may not be viable at one site or even within one district.

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Additionally, the inter-relationship between the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation is not specified. This lack of boundary limits and control frequently presents difficulties for manufacturers of IVD products.

Threshold levels for enforcement action need additional review. It does not appear that risk to public health and the class of the device were considered during the definition phase. For example, a large IVD firm may experience more than two after-sale product corrective actions during a twelve month period, none of which present any health risk. It is not reasonable to use one standard across all medical devices, which range from human implanted devices through unassayed quality control materials used by laboratory professionals.

Again, Beckman Coulter appreciates the opportunity to comment on this proposed guidance. Any questions regarding the comments provided in this letter or the attached table can be addressed to my attention at the letterhead address.

Sincerely,

Vlad Ghiulamila
Manager
Global Regulatory Compliance

RJO/VG:raf

Attachment: Table of Comments

Draft Compliance Guidance Manual: Inspection of Medical Devices

Comments by Beckman Coulter, Inc.

Second Release for Comments: from Federal Registerdated August 12, 1999

SECTION	CURRENT TEXT	SUGGESTED CHANGE	COMMENT
Part I - Preamble	Under the QS/GMP regulation, manufacturers are expected to control their products from birth to death, meaning from design stage through post-market surveillance.	Under the QS/GMP regulation, manufacturers are expected to control the design and production of their products, and when applicable, investigate complaints to monitor the performance of their products in the field after sale.	The statement that manufacturers are expected to control their products from "birth to death" is extremely hyperbolic and subject to misinterpretation. The subsequent statement, referring to design through post-market surveillance, provides helpful clarification, but is still misleading. The statement that manufacturers are responsible for their products from birth through death is similar to the statement used by the EPA that manufacturers must manage their wastes from the cradle to the grave, meaning that manufacturers are responsible for the proper disposal of their wastes and may be interpreted as obligating manufacturers, among other things, to provide maintenance and repair or accept the products for disposal after they are used. The statement that manufacturers must control their products through post-market surveillance could be interpreted as creating a higher level of performance than the current QS/GMP regulation requires. Under the current regulation, manufacturers are only obligated to investigate complaints, when appropriate, and track certain devices. To the extent that this statement is intended to refer to requirements such as medical device reporting, these requirements are not part of the QS/GMP regulation.

SECTION	CURRENT TEXT	SUGGESTED CHANGE	COMMENT
Part I - Section A [third paragraph)	The "top-down" inspectional approach begins looking at a firm's "systems" for addressing quality problems, as opposed to a "bottom-up" approach, which starts by looking at one or more problems that may point to a failure in the quality system.	The "top-down" inspectional approach begins looking at a firm's "systems" for designing and manufacturing products which are safe and effective for their intended use. It is intended to verify that the firm's systems are appropriate for the type of products it designs and/or manufactures and that the systems are followed.	The revised statement sets the tone of the inspection in a more positive light. The statement that the purpose of the inspection is to look at a firm's system for addressing "quality problems" misstates the purpose of both the QS/GMP regulation and the inspection. Basically, it assumes that the firm has quality problems which must be identified and addressed. The QS/GMP regulation is structured to encourage firms to put systems in place which assure that products are designed and manufactured in a way that prevents quality problems.
Part II - Section B.1.b.	Many large firms have several manufacturing facilities located in more than one district. These firms often have a research and development (R&D) center or corporate design facility which services several manufacturing facilities.	Many large firms have centralized research and development and product design facilities which also are responsible for evaluating complaints and overseeing their investigation. Products may be manufactured at separate manufacturing facilities located in different districts and several facilities may manufacture the same products.	Many large firms have centralized product development operations. Design control activities and the related records are found at these locations. Product manufacturing may take place at different locations and, depending on volume and other factors, the same product may be manufactured at more than one location. In these firms, complaint investigation and tracking also is centralized in the product development center. The technical expertise resides at this location and the center may see events involving products manufactured at multiple facilities. In this context, the manufacturing facility's role may be limited to providing lot-specific information, such as verifying that processing parameters were acceptable and testing retained samples of raw materials and completed products. FDA needs to ensure that inspectors understand and respect these differences. Inspectors should not expect complete design history files or complaint investigation materials to be available at the manufacturing facility if it

SECTION	CURRENT TEXT	SUGGESTED CHANGE	COMMENT
Part II - Section B.I .b. 'Continued)			s not engaged in those activities. In addition, in order o avoid duplicative inspections, inspectors should not ask the manufacturing facility to obtain and provide' hese materials.
Part II - Section B. 1 .b.	Jnless additional nformation must be obtained from the manufacturing facility, the home district of the manufacturing facility will not need to conduct a routine design control assessment if an inspection of the R&D center or corporate design facility was conducted within the previous two years.	The home district of the nanufacturing facility is not esponsible for conducting design control assessments of the products manufactured at the facility. Similarly, if the nanufacturing facility is not esponsible for investigating complaints, then the home district of the manufacturing facility is not responsible for nvestigating the firm's complaint handling procedures.	The statement that inspectors should not conduct design review of manufacturing facilities unless additional information must be obtained is confusing snd potentially misleading. It is not clear from this statement what types of information inspectors at a manufacturing facility will be expected to obtain; therefore, the facility cannot anticipate what types of information it must be able to provide. In addition, in many large firms, both product development and complaint investigation activities are conducted at a centralized facility. The manufacturing facility's role may be limited to providing lot-specific information, such as verifying that processing parameters were acceptable and testing retained samples of raw materials and completed products. In these cases, review of the complaint investigation activities as well as design control activities should be referred to the district where the activities are actually conducted. Inspectors should not expect complete design history files or complaint investigation materials to be available at the manufacturing facility if it is not engaged in those activities. In addition, in order to avoid duplicative inspections, inspectors should not ask the manufacturing facility to obtain and provide these materials.

SECTION	CURRENT TEXT	SUGGESTED CHANGE	COMMENT
Part II - Section B.l .d.	Medical Devices related to AIDS diagnosis, blood banking and/or human blood processing will be inspected under this compliance program.	Medical Devices related to AIDS diagnosis and screening, blood banking, and/or human blood processing will be inspected under this compliance program.	This is a useful clarification regarding the inspectional process for these products. One question the text raises is whether devices related to AIDS screening of the blood supply also will be inspected under this program. It would also be helpful if FDA clarified if these inspections are to be performed by CDRH or CBER.
Part II - Section B.2.a.; Priority B, #3	Manufacturers of Class II or I devices that have conducted more than two recalls in the last 12 months.	Manufacturers of Class II or I devices that have multiple recalls in the last 12 months involving the same device classification and the same failure mode. The criteria should take into account the number and complexity of the products.	It is not clear why FDA has chosen two recalls in a twelve-month period as the threshold for placing a manufacturer in Priority B. Many large firms, especially those who sell in vitro diagnostic products, manufacture multiple lots of a broad variety of products in several device classifications. It would not be unusual for those manufacturers to have two recalls in a year. Consequently, at a minimum, FDA should modify the statement to specify that the recalls must involve products in the same device classification.
Part II - Section B.2.a; Priority B, #4	Manufacturers of Class II or I devices that have recently experienced an increase in MDR reports.	Manufacturers of Class II or I devices that have recently experienced a significant increase in MDR reports involving products in the same device classification, taking into account the volume of sales and nature of the product.	FDA needs to clarify how this criteria is intended to work. For example, how large of an increase on MDR reports is enough to trigger the criteria? Similarly, must the increase involve all of the firm's products or only those in one device classification? Who at FDA tracks MDR reports and makes this determination? Many large firms, especially those who sell in vitro diagnostic products, manufacture multiple lots of a broad variety of products in several device classifications. It would not be unusual for those manufacturers to have varying levels of MDR reports. At a minimum, FDA should modify the statement to specify that the reports must involve products in the same device classification.

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Part II - Section B.2.a; (last paragraph)	QS/GMP inspectional coverage will be focused on that segment of the industry that is actively bringing devices to market and thus presenting the most risk to the public.	QS/GMP inspectional coverage of design control activities will be focused on that segment of the industry that is actively bringing devices to market and thus is actively engaged in product design activities.	Devices are eligible for the 510(K) process only if FDA has determined that they are relatively low risk and use existing, established technologies. The assertion that these firms are "presenting the most risk to the public" is misleading because it implies that devices brought to market through the 510(k) process are inherently less safe than other types of devices.
Part III - Section A.1. a.; LEVEL 1 Inspections	Level 1 inspections can be done at the district's discretion on firms that passed a previous Baseline inspection and those where the last inspection was classified VAI or NAI.	Level 1 inspections can be done at the district's discretion on firms that were not issued a Form 483, following the previous Baseline inspection or where the last inspection was classified VAI or NAI.	The word "passed" is not defined.
Part III - Section A.1 .a.; LEVEL 1 Inspections	Prior to deciding which subsystems to inspect (in addition to the CAPA subsystem) determine if there were: • Changes in management control procedures • Management control changes • Changes in design control procedures • Design changes • Changes in production and process control procedures • Production and process changes		The text lists six types of changes that the inspector should consider in deciding which subsystems to inspect. However, the guidance does not explain why these particular types of changes are significant, what the inspector is to do with the information, or how the inspector is to use this information to select subsystems to inspect. Nor does it provide any guidance on how to rank the changes should the firm have made more than one of the listed changes.

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Part III - Section A.1 .a.; LEVEL 3 Inspections	. ..(B) if the corrections were not made, verify that the violations continue to exist, and provide adequate evidence to support a possible regulatory action.	...(B) if the corrections were not made, verify that the firm is continuing to take steps to correct the violations. If the violations continue to exist and appropriate corrective actions are not being taken, provide adequate evidence to support a possible regulatory action.	The quoted text is somewhat incomplete. If the violations do not continue to exist, then corrective actions must have been taken, although perhaps not the specific ones promised in the response to the warning letter. Also, the text does not address what to do if the corrective actions have not been completed but the firm is continuing to take action to complete the corrections.
Part III – Section A.4.	Should you have questions regarding the need to collect samples related to the sterilization process, you should contact Sarah Mowitt at (301) 594-4595.		This document is full of references to specifically named individuals with addresses and telephone numbers. Some of them are already out of date. It would be more efficient to put information such as this on the FDA web site. Otherwise, the document is going to be immediately outdated, and not totally useful to the FDA personnel.
Part III - Section D.4.	If a firm has failed to list device(s) or update listing every six months as required by 21 CFR Part 807, you should place the observations on the form FDA-483. Do not cite an establishment for failure to reregister unless it has not done so for two or more years.	If a firm has failed to list device(s) or update listing as required by 21 CFR Part 807, you should...	Part 807 does not require listings to be updated every six months. It states that updates may be provided as they occur or twice per year, in June and December.

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Part V- Section A.1 .a.; [fifth bullet)	An excessive number of minor non-conformities against the Quality System requirements, either found in more than one subsystem or that are repeat deficiencies that may be indicating a trend, and uncorrected could become a major non-conformity, or could be related to potential product failures.		The definition of what constitutes major and minor non-conformities must be defined in a way that will be clear and unambiguous for FDA investigators and for industry. Beckman Coulter believes it would be appropriate to define as major those situations where entire subsystems are lacking and to define as minor those situations which involve isolated events or episodes.
Part V - Section 5.A.1.; Chart A	The examples of Situation 1 violations below are for illustrative purposes only. There are many other possible examples.		Remove Chart A. It appears to treat portions of the regulations with greater weight than others.
Part V - Section A.4.	Consequently, when FDA recommends against acceptance of a device by a government agency because that device, or its manufacturer, is in violation of the FD&C Act, FDA shall also include appropriate regulatory/administrative action against the same or similar device sold to commercial accounts.	Consequently, FDA shall not recommend against acceptance of a device by a government agency because that device, or its manufacturer, is in violation of the FD&C Act, unless FDA also has initiated appropriate regulatory/administrative action.. . .	This sounds like the reinstatement of a reference list. If FDA already has determined that the level of noncompliance is sufficient to initiate enforcement action, then its recommendation against acceptance would be consistent with its position and would follow from its actions.

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PartV-Section A.5.c.(2)(a)	This Warning Letter requests the manufacturer to submit to the district (for up to 2 years if the district believes that it is necessary) an annual certification by an outside expert consultant stating that it has conducted a complete audit of the establishment's manufacturing, quality assurance (and if applicable, design control) systems relative to the requirements of the Quality System regulation.	This Warning Letter mandates that the manufacturer submit.. . .	Beckman Coulter questions whether a Warning Letter is the appropriate vehicle for this type of action. FDA appropriately couches the action as a "request"; however, the Warning Letter is a unilateral document directed from FDA to the manufacturer.
PartV-Section A.5.g.	A citation should be recommended if appropriate as stated in Chapter 5 of the RPM.		Beckman Coulter is unfamiliar with this type of regulatory action.
PartV-Section A.6.b.	When the district knows a regulatory action will be forthcoming as a result of the inspection, it should FAX a copy of the issued Form-484 to the appropriate division in OC.	When the district believes that a regulatory action will be forthcoming.. . .	The implication of the other paragraphs of Section V.6. is that the decision to initiate a regulatory action is the result of a consultative process between the District and CDRH. Consequently, it is not clear how the District would "know" that an action is forthcoming at this point.

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